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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/461,090	12/14/99	ULLRICH	A P564-9051

HM12/0518

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EXAMINER	
LU,F	
ART UNIT	PAPER NUMBER
1655	11

DATE MAILED: 05/18/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/461,090	Ullrich et al.,
Examiner	**Art Unit**
Frank Lu	1655

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *12/13/1999. 12/18/2000, and 3/6/2001* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-21* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Response to Amendment

1. Applicant's response to the office action filed on December 13, 2000, December 18, 2000, and a supplemental amendment filed on March 6, 2001 has been entered as Paper Nos: 8-10. The claims pending in this application are claims 1-21. Rejection and or objection not reiterated from the previous office action are hereby withdrawn. The following rejections are based on amendment.

Drawings

2. The drawings remains objected to for reasons as stated on FORM PTO-948 (Rev. 8-98). Applicant is required to submit a proposed drawing correction in reply to this Office action. However, formal correction of the noted defect can be deferred until the application is allowed by the examiner. The examiner noticed that applicant did not address this issue.

Claim Rejections - 35 U.S.C. § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 17, 18, and 21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for modulating growth-factor activation

with a modulator of G-protein mediated signal transduction in *in vitro*, does not reasonably provide enablement for: (1) a method for modulating growth-factor activation in an organism comprising a cell which contains a growth-factor receptor capable of being activated with a modulator of G-protein mediated signal transduction; and (2) using a method for modulating growth-factor activation comprising contacting a cell which contains a growth-factor receptor capable of being activated with a modulator of G-protein mediated signal transduction in the prevention or treatment of disorders associated with a disturbed growth factor receptor activation such as cancer or asthma as described in claims 17, 18, and 21. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims without undue experimentation.

In *In re Wands*, 858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court considered the issue of enablement in molecular biology. The Court summarized eight factors to be considered in a determination of "undue experimentation". These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims. The Court also stated that although the level of skill in molecular biology is high, results of experiments in molecular biology are unpredictable.

To begin, there is no direction or guidance on how to modulate growth-factor activation in an organism comprising a cell which contains a growth-factor receptor capable of being activated with a modulator of G-protein mediated signal transduction and use a method for

modulating growth-factor activation comprising contacting a cell which contains a growth-factor receptor capable of being activated with a modulator of G-protein mediated signal transduction in the prevention or treatment of disorders associated with a disturbed growth factor receptor activation such as cancer or asthma as described in claims 17, 18, and 21. While the relative skill in the art is very high (the Ph.D. degree with laboratory experience), there is no predictability whether a method for modulating growth-factor activation comprising contacting a cell which contains a growth-factor receptor capable of being activated with a modulator of G-protein mediated signal transduction in *in vitro* can be used in an organism comprising a cell which contains a growth-factor receptor capable of being activated with a modulator of G-protein mediated signal transduction and can be used in the prevention or treatment of disorders associated with a disturbed growth factor receptor activation such as cancer or asthma.

The specification (pages 9-17) provides adequate guidance for a method for modulating growth-factor activation comprising contacting a cell which contains a growth-factor receptor capable of being activated with a modulator of G-protein mediated signal transduction in *in vitro.* Since it has been well known in the art that research *in vitro* could provide a direction for in *vivo* study and a method for using a drug that worked in *in vitro* for treating certain disease such as cancer, in the most time, does not work or work efficiently in human body, there will be a lot of unpredictable factors when the skilled artisan uses the method for modulating growth factor activation *in vitro* in an organism comprising a cell which contains a growth-factor receptor capable of being activated with a modulator of G-protein mediated signal transduction and in the prevention or treatment of disorders associated with growth factor receptor such as the treatment

of cancer or asthma and the skilled artisan will have no way to predict the experimental results. With the predictability in the relevant art being low, the amount of experimentation needed to be exerted by the public in practicing the full scope of the invention would not fall within the limits of routine experimentation. Such efforts constitute undue experimentation. The situation at hand is analogous to that in *Genentech v. Novo Nordisk A/S* 42 USPQ2d 1001 (see above). As set forth in the decision of the Court:

> " '[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.' *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *see also Amgen Inc. v. Chugai Pharms. Co.*, 927 F. 2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed Cir. 1991); *In re Fisher*, 427 F. 2d 833, 166 USPQ 18, 24 (CCPA 1970) ('[T]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.').
> "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. *See Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (starting, in context of the utility requirement, that 'a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.') Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.
> "It is true . . . that a specification need not disclose what is well known in the art. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skill in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

Accordingly, it is concluded that undue experimentation is required to make the invention as it is claimed. See M.P.E.P. 706.03(n) and 706.03(z).

Response to Arguments

In page 4, first paragraph of applicant's remarks filed on December 13, 2000, applicant argued that "no evidence has been submitted which demonstrates any reason to doubt a reasonable correlation between the in vitro example and *in vivo* activity for the claimed invention. Nor has any evidence been present which indicates that those of skill in the art would be unable to determine dosage amounts from the disclosure of the application including the *in vitro* examples".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, the examiner does not need to provide evidence but reasons to support his position. In contract, applicants need to provide evidence to support their claimed invention. Second, it has been well known in the art that research *in vitro* could provide a direction for in *vivo* study and a method for using a drug that worked in *in vitro* for treating certain disease such as cancer, in the most time, does not work or work efficiently in human body. Therefore, there will be a lot of unpredictable factors when the skilled artisan uses the method for modulating growth factor activation *in vitro* in the prevention or treatment of disorders associated with growth factor receptor such as the treatment of cancer or asthma and the skilled artisan will have no way to predict the experimental results. With the predictability in the relevant art being low, the amount of experimentation needed to be exerted by the public in

practicing the full scope of the invention would not fall within the limits of routine experimentation. Such efforts constitute undue experimentation. The situation at hand is analogous to that in *Genentech v. Novo Nordisk A/S* 42 USPQ2d 1001 (see above).

Claim Rejections - 35 U.S.C. § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1, 3-6, 16, 19, and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Daub *et al.*, (EMBO. J. 16, 7032-7044, December 1997).

Daub *et al.,* teach signal characteristics of G protein-transactivated EGF receptor. As acknowledged by Daub *et al.,* the epidermal growth factor receptor (EGFR) is known as an essential link in the GPCR-mediated MAPK activation pathway in Rat-1 fibroblasts treated with the GPCR agonists ET-1, LPA or thrombin (page 7032, right column, second paragraph). This cross-talk pathway was also established in different cell types such as HaCaT keratinocytes, primary mouse astrocytes and COS-7 cells (page 7032, abstract). In this study, different cell types were stimulated with different modulator or test compound which include endogenous GPCR signal events such as LPA, thrombin, TRP, and EGR as described in claims 1, 3-6, 16, and 20. After lysing the cells, EGFR was immunoprecipitated using polyclonal anti-EGFR

antibody. Immunoblotting was done with anti-phosphotyrosine mAb, followed by reprobing with anti-EGFR antibody (page 7033, the Figure legend of Figure 1). As shown in Figure 1A, stimulation of human HaCaT keratinocytes with thrombin or LPA resulted in enhanced tyrosine phosphorylation of endogenous EGFR. In addition, thrombin or extracellularly applied ATP triggered a comparable response in primary mouse astrocytes (Figure 1B). Thrombin and LPA were also effective in COS-7 cells, where these GPCR ligands stimulated tyrosine phosphorylation of endogenous EGFR to a similar extent as 1-3 ng/ml EGF (Figure 1C) (page 7033, left column, second paragraph). Note that, although Daub *et al.,* did not show that the activation of EGF receptor was mediated by its extracellular domain as described claim 1, in the absence of convincing evidence to the contrary the claimed invention, this limitation is considered as inherent to the reference taught by Daub *et al.,* since the method taught by Daub *et al.,*could transactivate EGF receptor by G protein-couple receptor even they did not known that this process was mediated by its extracellular domain.

Therefore, Daub *et al.,* teach all limitation recited by claims 1, 3-6, 16, 19, and 20.

7. Claims 1, 3-16, 19, and 20 are rejected under 35 U.S.C. 102(a) as being anticipated by Dong *et al.,* (Proc. Natl. Acad. Sci. USA, 96, 6235-6240, May 1999) .

Dong *et al.,* teach metalloprotease-mediated ligand release regulates autocrine signaling through the epidermal growth factor receptor. As acknowledged by Dong *et al.,* ligands that activated the epidermal growth factor receptor (EGFR) were synthesized as membrane-anchored precursors that appeared to be proteolytically released by members of the

ADAM family of metalloproteases. This membrane-anchored EGFR ligands were thought to be biologically. In this study, they used metalloprotease inhibitors to block EGFR ligand release from human mammary epithelial cells. These cells expressed both transforming growth factor α and amphiregulin and required autocrine signaling through the EGFR (extracellular domain) for proliferation and migration. They found that a metalloprotease inhibitor, batimastat (see page 6236, Figure 1), reduced cell proliferation in direct proportion to their effect on transforming growth factor α release. This metalloprotease inhibitor also reduced growth of EGF-responsive tumorigenic cell lines and were synergistic with the inhibitory effects of antagonistic EGFR antibodies. Blocking release of EGFR ligands also strongly inhibited autocrine activation of the EGFR and reduced both the rate and persistence of cell migration. The effects of this metalloprotease inhibitor could be reversed by either adding exogenous EGF or by expressing an artificial gene for EGF that lacked a membrane-anchoring domain (page 6235, abstract). The effect of batimastat on the activation of tyosine phosphorylation was also be examined (see page 6238, right column and Figure 4). Note that "capable of being activated with a modulator of G-protein mediated signal transduction" in claim 1 and "capable of being activated with a test compound suspected to be a modulator of G-protein mediated signal transduction and determining the degree of growth-factor receptor activation" in claim 20 could be considered optional, epidermal growth factor receptor taught by Dong *et al.*, has this property.

Therefore, Daub *et al.*, teach all limitation recited by claims 1, 3-16, 19, and 20.

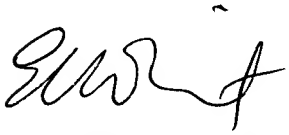
9. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is either (703) 308-4242 or (703)305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (703) 305-1270. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the Chemical Matrix receptionist whose telephone number is (703) 308-0196.

Frank Lu
May 16, 2001



Ethan Whisenant, Ph.D.
Primary Examiner (FSA)